REMARKS

The Invention

The invention is a functional origin of replication comprising the replication sequences, genes and proteins that make possible the replication of extrachromosomal elements in *Fusobacterium* species. The invention further comprises a series of plasmids bearing this origin that replicate in *Fusobacterium* species and a shuttle vector that replicates in *Escherichia coli* as well as *Fusobacterium*. Finally the invention provides, for the first time, methods for the transformation of *Fusobacterium* species with plasmids.

Status of the Claims

Claims 1-63 are pending. Claims 1-9 and 12-63 are rejected. Claims 10 and 11 are allowed.

Claims 1, 4, 33, 35, 40 and claims 58-60 are objected to because of informalities in their wording.

Claims 35, 36, and 48 are rejected under 35 U.S.C. §112 first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. Claims 1-9, 12-32, 37-47 and 49-63 are rejected under 35 U.S.C. §112 second paragraph, as failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention.

Claims 5-9, 15-17, 21-23, 27-29, 33 and 34 are rejected under 35 USC §102(a) as being anticipated by Kinder Haake *et al.* (Journal of Dental Research 78 (abstracts):420, abstract No. 2498, 1999). Claims 5-9, 15-34, 37-45 and 47-63 are also rejected under 35 U.S.C. §102(a) as being anticipated by Kinder Haake *et al.* (Abstracts of the General Meeting of the American Society of Microbiology 99:331, Abstract No. H-9, May 1999).

Claims 5, 7 and 8 are rejected under 35 U.S.C. §102(b) as being anticipated by McKay *et al.* (Plasmid 33:15-25 1995).

The Amendments

The claims have been amended to address the objections and rejections raised by the Examiner.

The Examiner's objections to claims 1, 4, 33, 35, 40 are based on informalities or incorrect grammar. Claims 58 and 60 were objected to based on the fact that the claims were duplicates of one another. All these objections have been addressed by the amendments. The specific changes are discussed in the Objections section below. The scope of the claims is not changed by the amendments, and no new matter is added.

Claims 1-9, 12-32, 37-47 and 49-63 are rejected under 35 U.S.C. §112 second paragraph.

Claims 1, 5, 12, 21, 27 and 41 are amended to clarify that the plasmid was functional in *F. nucleatum*. Claims 2-3, 6-9, 13-14, 22-25, 28-32, and 42-47 are dependent on claims 1, 5, 12, 21, 27 and 41, respectively. Thus, amendment of claims 1, 5, 12, 21, 27 and 41 also amends claims 2-3, 6-9, 13-14, 22-25, 28-32, and 42-47. The specifics of the amendments are discussed in detail under the section entitled "Rejection Under 35 U.S.C. 35 §112, Second Paragraph". The scope of the claims is not changed by the amendments, and no new matter is added.

Claims 5, 21, 27 and 41 are amended to clarify that a protein and not a nucleic acid binds polyclonal antibodies. Claims 6-9, 22-25, 28-32, and 42-47 are dependent on claims 5, 21, 27 and 41, respectively. Thus, amendment of claims 5, 21, 27 and 41 also amends claims 2-3, 22-25, 28-32, and 42-47. The specifics of the amendments are also discussed in detail under the section entitled "Rejection Under 35 U.S.C. 35 §112, Second Paragraph". The scope of the claims is not changed by the amendments, and no new matter is added.

Claim 12 is amended to replace "having" with "comprising" in line 2, and "selectively binding" with "a protein that is selectively bound by" in step (b). Again, claims 13-14 which are dependent on claim 12, are also clarified by this amendment. The scope of the claim is not changed by this amendment, and no new matter is added.

Claims 1, 5, 6, 9, 12-15, 21-23, 27-29, 37 and 41-43 are amended to replace "having" or "has" with "comprising", "comprised of", "comprises" or "consisting of" as appropriate. The amendment serves to clarify the claims by expressing them in open or closed language that is legally defined. The scope of the claims is not changed by the amendments, and no new matter is added.

Claim 26 has been amended to provide sufficient antecedent basis for a correct claim. The scope of the claim is not changed by this amendment, and no new matter is added.

Finally, claims 58-63 are amended to recite complete methods. Support for the amendment is found in the specification on page 34, lines 18-31, on page 40, lines 27-34, and page 41, lines 1-6. The scope of the claims is not changed by the amendments, and no new matter is added.

The Objections

The Examiner objected to claim 1 because it recites the abbreviation *F. nucleatum* in line 1 without prior definition. The claim has been amended to recite *Fusobacterium nucleatum* in line 1. Thus, *F. nucleatum* is now defined.

Claims 4, 33 and 40 are objected to because the sequences recited in the claims are not identified by a SEQ ID NO. The claims have now been amended to recite the appropriate SEQ ID NO.

Claim 35 is objected to for recitatition of the word "have" in a grammatically incorrect manner. The claim has been amended to recite "has" which is the grammatically correct form of to have in the context of the claim.

The Examiner objects that claims 58 and 60 are duplicate claims. Claim 60 has been amended to recite a method for transforming *F. nucleatum* with the plasmid of claim 33. Claim 58 still recites a method for transforming *F. nucleatum* with the plasmid of claim 15. Thus, the two claims are no longer duplicates of one another.

The Rejections

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 35, 36 and 48 because, the Examiner states, it is not clear that the identical plasmids are freely available or can be reproducibly isolated from nature. The Applicants respond that upon indication from the Examiner that the claims are otherwise allowable, Applicant will make deposits of the appropriate strains. Applicants further respond that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request; and

(b) all restrictions upon availability to the public will be removed upon granting of the patent.

After placing the strains in a recognized depository, the Applicant will provide:

(1) the name and address of the depository,

(2) the name and address of the depositor,

(3) the date of the deposit,

(4) the identity of the deposit and the accession number given by the depository,

(5) the date of the viability test,

(6) the procedures used to obtain the sample if the test is not done by the depository, and

(7) a statement that the deposit is capable of reproduction.

In addition, the Applicant will ensure that:

(8) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the granting of the last request, or for the effective life of the patent, whichever is longer; and

(9) the deposit will be replaced if it should ever become inviable.

Rejection Under 35 U.S.C. 35 §112, Second Paragraph

The Examiner rejects claims 1-9, 12-32, 37-47, and 49-63 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Applicants respond to these rejections by amending the claims to make clear which subject matter the Applicants regard as their invention.

Claims 1, 5, 12, 21, 27 and 41 were rejected because it was not clear whether the Applicants intended to mean that the plasmid was isolated **from** *F. nucleatum* or whether the Applicants intended to mean that the plasmid was **functional in** *F. nucleatum*. The claims have been amended to reflect that the Applicants intended to mean that the plasmids are **functional in** *F. nucleatum*. Those claims dependent on claims 1, 5, 12, 21, 27 and 41 are also clarified in their meaning by these amendments.

Claims 1, 5, 6, 9, 12-15, 21-23, 27-29, 37 and 41-43 were rejected for reciting the terms "has" or "having". These terms are not legally defined as opened or closed language and so the claims are deemed unclear. The Applicants respond by amending the claims to recite "comprising", "comprised of", "comprises" or "consisting of" as appropriate.

Claims 5, 21, 27 and 41 are rejected by the Examiner for reciting the phrase "...selectively binding to polyclonal antibodies..." in step (b). Since the claims are otherwise drawn to nucleic acid sequences, the claims are deemed unclear. Applicants respond by amending the claims to recite "...encoding a protein that is...bound by...". Thus, Applicants clarify that the nucleic acid itself does not bind polyclonal antibodies.

Claim 12 is rejected as being unclear because it recites "having", and also because it recites "selectively binding" in step (b). The Applicants respond by amending the claim to overcome the Examiner's rejection. The claim now recites "comprising" instead of "having". In place of "selectively binding" claim 12 has also been amended to recite "a protein that is selectively bound by", so that step (b) is now consistent with the claim preamble.

Claim 26 is rejected as lacking antecedent basis in the recitation of the phrase "...wherein the nucleic acid encoding a RepA protein...". The claim has been amended to recite "...wherein a nucleic acid encoding an *F. nucleatum* RepA protein...". It is now clear that the nucleic acid referred to in claim 26 is a nucleic acid encoding an *F. nucleatum* RepA protein.

Claims 58-63 are rejected for reciting incomplete methods. The claims have been amended to include positive process steps that relate back to the method recited in the preamble. Thus, it is now clear what constitutes the claimed method.

Rejection Under 35 U.S.C. §102(a)

The Examiner rejects claims 5-9, 15-17, 21-23, 27-29, 33 and 34 under 35 U.S.C. §102(a) as allegedly being anticipated by Kinder Haake *et al.* (Journal of Dental Research 78 (abstracts):420, abstract No. 2498, 1999). The Examiner also rejects claims 5-9, 15-34, 37-45 and 47-63 under 35 U.S.C. §102(a) as allegedly being anticipated by Kinder Haake *et al.* (Abstracts of the General Meeting of the American Society of Microbiology 99:331, Abstract No. H-9, May 1999).

The Applicants respond by submitting, with this response, a declaration under 35 U.S.C §1.132 stating that Susan A. Kinder Haake, Kara K. Podkaminer, Gwynne Attarian, and Sean C. Yoder are the true and only inventors. Furthermore, that the subject matter of the above referenced abstracts represents the inventors' own work, and that others named in the above referenced abstracts did not contribute to the conception of the invention. Thus, the Examiner's rejection is overcome because the above cited abstracts are the Applicants' own work.

Rejection Under 35 U.S.C. §102(b)

The Examiner alleges that claims 5, 7 and 8 are anticipated under 35 U.S.C. §102(b) by McKay *et al.* (Plasmid 33:15-25 1995). The Examiner states that the plasmids of McKay *et al.* comprise a nucleic acid encoding a protein with 97.2%

sequence identity to SEQ ID NO:1 (RepA). The Examiner further states that "[T]he RepA protein disclosed by McKay *et al.* would intrinsically have the following properties: a molecular weight of 44.8 kilodaltons and the ability to selectively bind polyclonal antibodies generated against SEQ ID NO:1."

The Applicants respond that McKay *et al.* did not characterize their plasmids to a level sufficient for the identification and isolation of *individual* plasmid components. Thus, McKay *et al.* do not disclose a nucleic acid encoding a protein with 97.2% sequence identity to SEQ ID NO:1 (RepA) nor do they disclose a RepA protein with a molecular weight of 44.8 kilodaltons and the ability to selectively bind polyclonal antibodies generated against SEQ ID NO:1. Thus, the reference does not teach each and every element of the Applicants' claims.

While it may be assumed that any plasmid isolated from *Fusobacterium* is capable of replicating in *Fusobacterium*, McKay *et al.* did not identify or characterize the ***individual*** plasmid components necessary for the plasmids to replicate or otherwise function. McKay *et al.* extended their analysis only as far as their restriction digests. None of the components of the plasmids (*e.g.* replication proteins and replication origins) were characterized as to location, sequence composition, or function. In contrast, the Applicants fully characterized their plasmids. They provided full DNA sequences of the plasmid pFN1 and the shuttle vector pSH17, derived from it. The Applicants specifically identified the RepA protein and nucleic acid sequences. They identified and characterized the replication origin to which the RepA protein binds. They isolated and manipulated the repA nucleic acid sequence and created a shuttle vector by combining the repA nucleic acid into a heterologous plasmid. Thus, the Applicants' provide a detailed description of how isolate and use the RepA nucleic acid of *Fusobacterium* to create cloning vectors for *Fusobacterium*. In contrast, McKay *et al.* provide only a superficial restriction analysis of some naturally occurring plasmids.

The claims are to "an isolated nucleic acid encoding a RepA protein functional in *F. nucleatum*..." The meaning of the term isolated is defined in the

specification, on page 7, lines 16-26. In particular, lines 21-23 define an isolated repA nucleic acid: "... an isolated repA nucleic acid is ***separated*** from open reading frames that flank the repA gene and encode proteins other than the repA protein." (emphasis added). Thus, the **McKay *et al.*** reference does not anticipate the invention because it **does not disclose an isolated nucleic acid encoding a repA protein**.

In conclusion, the McKay *et al.* reference does not anticipate the Applicants' invention because McKay *et al.* did not distinguish the particular features of their plasmids and thus, they do not disclose the existence of a RepA protein with the characteristics of SEQ ID NO:1 either explicitly or implicitly. The Examiner's rejection is overcome because McKay *et al.* do not teach each and every element of the Applicants' claims.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Kenneth A. Weber
Reg. No. 31,677

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
ERS
SF 1315270 v3

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) An isolated origin of replication [for] functional in *Fusobacterium nucleatum* that comprises at least two copies of an iteron, the iteron [having] comprising a nucleic acid sequence of SEQ ID NO:3.

4. (amended) The isolated nucleic acid of claim 1, wherein the isolated origin of replication comprises a nucleic acid sequence of nucleotide position 3936 to 4481 of [plasmid pFN1] SEQ ID NO:6.

5. (amended) An isolated nucleic acid encoding a RepA protein [for] functional in *F. nucleatum*, the nucleic acid:

(a) encoding a protein [that has] comprising greater than about 80% amino acid sequence identity to SEQ ID NO:1; or

(b) encoding a protein that is selectively [binding to] bound by polyclonal antibodies generated against SEQ ID NO:1.

6. (amended) The isolated nucleic acid of claim 5, wherein the nucleic acid encodes a polypeptide [having a sequence of] comprising SEQ ID NO:1.

10. (amended) An isolated nucleic acid molecule comprising a 2.36 kb DNA fragment generated by [cleaving] cleavage of [plasmid pFN1] SEQ ID NO:6 with restriction endonucleases *Avr*II and *Sca*II.

12. (amended) An isolated RepA protein [for] functional in *F. nucleatum*, the RepA protein [having] comprising;

(a) greater than about 80% amino acid sequence identity to [a polypeptide having a sequence of] SEQ ID NO:1; or

(b) a protein that is selectively [binding to] bound by polyclonal antibodies generated against SEQ ID NO:1.

13. (amended) The isolated RepA protein of claim 12, wherein the polypeptide [has] comprises greater than about 97% sequence identity to [a polypeptide having a sequence of] SEQ ID NO:1.

14. (amended) The isolated RepA protein of claim 12, wherein the polypeptide [has the amino acid sequence of] is SEQ ID NO:1.

15. (amended) An isolated plasmid for replicating in *F. nucleatum*, the plasmid comprising an origin of replication that comprises at least two copies of an iteron, the iteron [having a] comprising the nucleic acid sequence of SEQ ID NO:3.

21. (amended) An isolated plasmid for replicating in *F. nucleatum*, the plasmid comprising a nucleic acid encoding a RepA protein [for] functional in *F. nucleatum*, the nucleic acid:

(a) encoding a protein [that has] comprising greater than about 80% amino acid sequence identity to [a polypeptide having a sequence of] SEQ ID NO:1; or

(b) encoding a protein that is selectively [binding to] bound by polyclonal antibodies generated against SEQ ID NO:1,

provided that the nucleic acid encoding the RepA protein [has other than the nucleic acid sequence of] is not SEQ ID NO:5.

22. (amended) The plasmid of claim 21, wherein the nucleic acid encodes a polypeptide [having a sequence of] comprising SEQ ID NO:1.

23. (amended) The plasmid of claim 21, wherein the nucleic acid [has a sequence of] comprises SEQ ID NO:2.

26. (amended) The plasmid of claim 20, wherein [the] a nucleic acid encoding an *F. nucleatum* RepA protein is recombinantly inserted into the plasmid.

27. (amended) The plasmid of claim 15, the plasmid further comprising a nucleic acid encoding a RepA protein [for] functional in *F. nucleatum*, the nucleic acid:

(a) encoding a protein that [has] comprises greater than about 80% amino acid sequence identity to [a polypeptide having a sequence of] SEQ ID NO:1; or

(b) encoding a protein that is selectively [binding to] bound by polyclonal antibodies generated against SEQ ID NO:1,

provided that the nucleic acid encoding the RepA protein [has other than the nucleic acid sequence of] is not SEQ ID NO:5.

28. (amended) The plasmid of claim 27, wherein the nucleic acid encodes a polypeptide [having a sequence of] comprising SEQ ID NO:1.

29. (amended) The plasmid of claim 27, wherein the nucleic acid [has a sequence of] comprises SEQ ID NO:2.

33. (amended) An isolated plasmid for replicating in *F. nucleatum*, the plasmid comprising:

(a) a nucleic acid sequence of nucleotide position 3936 to 4481 of [plasmid pFN1] SEQ ID NO:6;

(b) a 2.36 kb DNA fragment generated by cleaving [plasmid pFN1] SEQ ID NO:6 with restriction endonucleases Avr II and ScaII; or

(c) a 0.9 kb DNA fragment generated by cleaving plasmid pFN2 with restriction endonucleases HincII and HpaII

35. (amended) An isolated plasmid designated pFN2 that [have] has partial restriction maps as shown in Figure 1A, 3 and 5.

37. (amended) A shuttle vector comprising an origin of replication functional in *[E.] Escherichia coli* and an origin of replication functional in *F. nucleatum*, wherein the origin of replication functional in *F. nucleatum* comprises at least two copies of an iteron [having a nucleic acid sequence] comprised of SEQ ID NO:3.

40. (amended) The shuttle vector of claim 37, wherein the origin of replication functional in *F. nucleatum* comprises a nucleic acid sequence of nucleotide position 3936 to 4481 of [plasmid pFN1] SEQ ID NO:6.

41. (amended) The shuttle vector of claim 37, the vector further comprising a nucleic acid encoding a RepA protein [for] functional in *F. nucleatum*, the nucleic acid:

(a) encoding a protein that [has] comprises greater than about 80% amino acid sequence identity to [a polypeptide having a sequence of] SEQ ID NO:1; or

(b) encoding a protein that is selectively [binding to] bound by polyclonal antibodies generated against SEQ ID NO:1.

42. (amended) The shuttle vector of claim 41, wherein the nucleic acid encoding the RepA protein [for] functional in *F. nucleatum* encodes a polypeptide [having a] comprising SEQ ID NO:1.

43. (amended) The shuttle vector of claim 41, wherein the nucleic acid encoding the RepA protein [for] functional in *F. nucleatum* [has a sequence of] comprises SEQ ID NO:2.

58. (amended) A method of transforming *F. nucleatum* with the plasmid of claim 21, the method comprising:

contacting the plasmid with *F. nucleatum* in liquid media under conditions that allow the plasmid to be internalized by *F. nucleatum* and thereby, creating transformants.

59. (amended) A method of transforming *F. nucleatum* with the plasmid of claim 15, the method comprising:

contacting the plasmid with *F. nucleatum* in liquid media under conditions that allow the plasmid to be internalized by *F. nucleatum* and thereby, creating transformants.

60. (amended) A method of transforming *F. nucleatum* with the plasmid of claim 33, the method comprising:

contacting the plasmid with *F. nucleatum* in liquid media under conditions that allow the plasmid to be internalized by *F. nucleatum* and thereby, creating transformants.

61. (amended) A method of transforming *F. nucleatum* with the plasmid of claim 27, the method comprising:

contacting the plasmid with *F. nucleatum* in liquid media under conditions that allow the plasmid to be internalized by *F. nucleatum* and thereby, creating transformants.

62. (amended) A method of transforming *F. nucleatum* with the shuttle vector of claim 37, the method comprising:

contacting the plasmid with *F. nucleatum* in liquid media under conditions that allow the plasmid to be internalized by *F. nucleatum* and thereby, creating transformants.

63. (amended) A method of transforming *F. nucleatum* with the shuttle vector of claim 37, the method comprising:

contacting the plasmid with *F. nucleatum* in liquid media under conditions that allow the plasmid to be internalized by *F. nucleatum* and thereby, creating transformants.